IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant(s):	Schumm et al.	**Docket No.:**	16026/9238-02
Serial No.:	10/769,579	**Group Art Unit:**	1634
Filing Date:	January 30, 2004	**Examiner:**	J.A. Goldberg
Title:	MULTIPLEX AMPLIFICATION OF SHORT TANDEM REPEAT LOCI		

DECLARATION OF CYNTHIA J. SPRECHER UNDER 37 CFR § 1.132

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

I, Cynthia Sprecher, do hereby declare and state the following:

1. I am a Project Manager of the Research and Development Department at Promega Corporation ("Promega"). I received a Bachelor of Science degree in Biology from Mankato State University, Mankato, Minnesota in 1978. I have worked in the field of molecular biology, specializing in the detection and analysis of length and sequence polymorphisms in genomic DNA since at least as early as 1991. A copy of my resume is attached hereto as Exhibit A. As noted in the resume, I have authored or co-authored at least 21 publications in the field of DNA typing.

2. I am a joint inventor, with James W. Schumm and Ann M. Lins, of at least some of the claimed subject matter of the above-identified patent application ("the present application"). I make this declaration in support of prosecution of the present application before the U.S. Patent and Trademark Office ("PTO").

3. I have read and understand the invention as disclosed in the present application, including the invention described by the presently pending claims. I understand that claims 21 and 24 are under consideration and have been rejected. I further understand that claim 21 is directed to a method of simultaneously determining the alleles present in at least three short tandem repeat

(STR) loci from one or more DNA samples, comprising obtaining at least one DNA sample to be analyzed, selecting a set of at least three STR loci of the DNA sample to be analyzed which can be amplified together, wherein the at least three STR loci in the set comprises at least three loci selected from a recited group of loci, co-amplifying the set of at least three loci in a multiplex amplification reaction, wherein the product of the reaction is a mixture of amplified alleles from each of the co-amplified loci in the set, and evaluating the amplified alleles in the mixture to determine the alleles present at each of the co-amplified loci in the set. I also understand that claim 24 is directed to a method of simultaneously determining the alleles present in at least four STR loci from one or more DNA samples, comprising obtaining at least one DNA sample to be analyzed, selecting a set of at least four STR loci of the DNA sample to be analyzed which can be amplified together, wherein the at least four STR loci in the set comprises at least four loci comprising HUMCSF1PO, HUMTPOX, HUMTH01 and HUMVWFA31, co-amplifying the set of at least two STR loci in a multiplex amplification reaction, wherein the product of the reaction is a mixture of amplified alleles from each of the co-amplified loci in the set, and evaluating the amplified alleles in the mixture to determine the alleles present at each of the co-amplified loci in the set.

4. I have reviewed an Office Action from the PTO, mailed January 26, 2007 ("the Office Action"). I understand that claims 21 and 24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over one or more of the following references: (a) Caskey (U.S. Patent No. 5,364,759), (b) loci from the GenBank database, including HUMTPOX, HUMVWFA31 and HUMCSF1PO, (c) Fregeau (BioTechniques, Vol. 15, No. 1, pp. 100-119 (1993)), (d) Kimpton (PCR Methods and Applications, Vol. 3, pp. 13-22 (1993)), (e) Urquhart (Int. J. Leg. Med., Vol. 107, pp. 13-20 (Aug. 1994)), and (f) Schumm (U.S. Patent No. 5,783,406). I have reviewed the above references and I am of the opinion that it would not have been obvious to one having ordinary skill in the art, at the time the application to which the present application claims priority was filed, to combine the disclosures of the cited references in order to result in the subject matter of the rejected claims.

5. In the Office Action, Caskey is cited as allegedly disclosing obtaining a DNA sample, amplifying STR sequences from the DNA sample, and evaluating the amplification products for

identification. However, the Examiner admits that Caskey does not specifically teach the recited locus combinations. The Examiner further asserts, however, that STR loci HUMTPOX, HUMVWFA31, HUMTH01 and HUMCSF1PO have been disclosed by GenBank. Fregeau is cited as teaching, among other things, a multiplex system for DNA typing with fluorescently tagged STR loci for human identification and primers for STR systems identical to those disclosed in the present application. While Kimpton and Urquhart are cited as describing multiplex amplification of polymorphic STR sequences of a number of loci, and a method of simultaneously determining the alleles present in at least two STR loci, respectively, the Examiner concedes that neither of these references discloses the claimed locus combinations. Finally, Schumm is cited as teaching an assay for detecting at least one STR sequence from DNA at a specific locus using an allelic ladder containing at least two STR sequences.

6. The Examiner essentially asserts that it would have been obvious to one having ordinary skill in the art, at the time the application to which the present application was filed, to combine the disclosures of Caskey, GenBank, Fregeau, Kimpton and/or Urquhart, or alternatively, Schumm, Fregeau, Kimpton and/or Urquhart, to result in the methods of the rejected claims. Although the Examiner has raised two separate obviousness rejections against claims 21 and 24, because the set of references applied to each rejection largely overlap and the Examiner's analysis is the same in each rejection, my statements set forth below apply equally to both rejections.

7. I disagree with the Examiner's conclusion that it would have been obvious to obtain the technical solutions defined by the rejected claims in light of the cited references and/or GenBank disclosure. It should be noted that at the time the application to which the present application claims priority was filed, few of the loci and none of the combinations of loci were "known," *per se*, to be useful for genetic identity purposes. The advantage of having additional loci and differing sets of loci is well-established. (*See, e.g.*, Kimpton, p. 13, Fregeau, pp. 108-109, and present application, p. 2, lines 2-30.) However, selection of the loci is not a trivial matter. It must be emphasized that discovery of the usefulness of the loci and combinations of loci claimed in the present application required inventive skill. In my experience, at the time the application to which the present application claims priority was filed, selecting STR loci for DNA typing,

and subsequently co-amplifying the selected STR loci in a multiplex reaction, was very laborious and unpredictable. It was virtually impossible to predict in advance which loci could be amplified and evaluated together in a multiplex reaction.

8. Further, despite extensive interest in multiplex PCR amplification and the development of some general guidelines, the process of selecting PCR primers to use in multiplex reactions from those that work well in individual PCR reactions was not predictable. In contemplating a new multiplex, one needed to evaluate each locus for utility and for technical feasibility and, even then, one still could not predict with any reasonable degree of certainty that any particular set of loci would be successful. That is, it was very possible that despite extensive trial and error, one having ordinary skill in the art would not have been successful in identifying useful multiplexes for DNA typing purposes. Accordingly, it should be appreciated that at the time the invention was made, it was not trivial to combine loci in a multiplex reaction.

9. In fact, the references themselves emphasize the difficulties associated with selecting loci to perform such a method. For example, one of the two sets of loci identified by Caskey were reported as producing problematic overlapping doublet bands on gel electrophoresis (*see* Caskey, Fig. 3) and Kimpton discloses that selection of STR loci is an important consideration as precision may be reduced if less compatible loci are co-amplified together (*see* Kimpton, p. 16, col. 3 to p. 17, col. 1). Thus, in light of the fact that the references actually disclose that selecting and co-amplifying any number of loci and simultaneously determining the alleles present is difficult, one having ordinary skill in the art would not have been motivated to combine the references to result in the methods of the rejected claims.

10. In summary, at the time the application to which the present application claims priority was filed, one having ordinary skill in the art could not predict with any reasonable expectation of success any of the claimed methods, which require selecting the claimed sets of STR loci capable of being co-amplified, co-amplifying sets of loci in a multiplex amplification reaction, and evaluating the amplified alleles in the set to determine the alleles present at each of the loci in the set. Thus, I submit that none of the references and/or disclosures cited in the Office Action combine to teach or suggest the methods as defined by claims 21 and 24.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 5/2/07

Cynthia J. Sprecher